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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BROOKS, KRISTIE LATRICE	
ART UNIT	**PAPER NUMBER**
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,008	BELANOFF, JOSEPH K.	
	Examiner	Art Unit	
	KRISTIE L. BROOKS	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Claims 1-19 are pending.

2. Receipt and consideration of Applicants remarks/arguments submitted on August 22, 2008 is acknowledged.

3. Rejections not reiterated from the previous Office Action are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1-4, 8-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schatzberg et al. (US 6,150, 349) in view of Ademmer et al. (Suicidal Ideation with IFN-α and Ribavirin in a Patient with Hepatitis C, *Psychosomatics* 42:4, 365-367, 2001).

Applicant claims a method of ameliorating the symptoms of psychosis associated with interferon-α therapy in a patient comprising administering to the patient having received interferon-α therapy and suffering from psychosis associated with the interferon- α therapy, an amount of a glucocorticoid receptor antagonist effective to ameliorate the symptoms of psychosis in the patient, with the proviso that the patient is not otherwise in need of treatment with a glucocorticoid receptor antagonist.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Schatzberg et al. teach a method of ameliorating psychosis to patient in need thereof, including the psychotic component of pathologies or conditions with psychotic symptoms (see the entire article, especially column 1 lines 19-21). The term "psychosis" can refer to a psychiatric condition or symptom associated with a medical condition, a disease state or other conditions such as a side effect of a medication or side effect of drug abuse (see the entire article, especially column 6 lines 25-32). The method of ameliorating psychosis, particularly psychosis associated with major depression, comprises administering an effective amount of a glucocorticoid receptor antagonist where the glucocorticoid receptor antagonist used in the methods can

comprise a steroidal skeleton with at least one phenyl-containing moiety in the 11-beta position of the steroidal skeleton where the phenyl-containing moiety in the 11-beta position of the steroidal skeleton can be a dimethylaminophenyl moiety and the glucocorticoid receptor antagonist can comprise mifepristone (RU486), 11-β-(4-dimethyl-aminoethoxyphenyl)-17α-propynyl- 17β-hydroxy-4,9-estradien-3-one(RU009), and 17β-hydrox-17α -19-(4-methyl-phenyl)androsta-4,9 (11)-dien-3-one (RU044) (see the entire article, especially column 3 lines 46-63; column 10 lines 7-21). The glucocorticoid antagonist can be administered by oral administration, topical administration, aerosol formulations, where the dosage of mifepristone can be about 2-30mg per kg of body weight per day (see the entire article, especially column 20 lines 25-45; column 21 lines 56-68).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Schatzberg et al. do not teach ameliorating the symptoms of psychosis associated with a patient having received interferon- α therapy and is suffering from psychosis associated with interferon-α therapy by administering a glucocorticoid receptor antagonist. Schatzberg et al. do not teach administering the glucocorticoid receptor antagonist in combination with interferon-α and a second therapeutic agent. These deficiencies are cured by the teaching of Ademmer et al.

Ademmer et al. teach the state of the art treatment for hepatitis C virus (HCV) is the combination therapy with interferon alpha (IFN- α) and ribavirin (see the entire article, especially the first paragraph in the first column). One of the most serious side effects of the IFN- α treatment is the development of psychiatric symptoms, particularly depression and suicidal ideation (see the entire article, especially the first paragraph in the first column on page 365). In a case report, a 55 year old, Mr. A with a chronic active infection of HCV, started on treatment with IFN- α and ribavirin (see the entire article, especially the first paragraph under the Case Report). Immediately after starting therapy Mr. A appeared to be depressed and became progressively isolated (see the entire article, especially the second paragraph under the Case Report in column 2 on page 365). After four months of receiving treatment for his hepatitis C infection, Mr. A was admitted to a psychosomatic ward where he met criteria for major depression (see the entire article, especially the last sentence in the second paragraph under the Case Report and the third paragraph under the Case Report on page 366).

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to ameliorate the symptoms of psychosis associated with a patient having received interferon- α therapy and is suffering from psychosis associated

with interferon-α therapy by administering a glucocorticoid receptor antagonist and to further administer the glucocorticoid receptor antagonist in combination with interferon-α and a second therapeutic agent.

One of ordinary skill in the art would have been motivated to do this Schatzberg et al. suggests the use of a glucocorticoid receptor antagonist for treating the symptoms of psychosis (e.g. major depression) caused by the side effects of a medication. Although Schatzberg et al. do not teach the specific medication for which side effects will occur, it is well known in the art that major side effects are associated with receiving IFN- α drug treatment which includes the development of psychiatric symptoms, such as major depression as taught by Ademmer et al. Thus, it would have been obvious to one of ordinary skill in the art because patients receiving IFN- α treatment are at risk for developing psychiatric symptoms and the glucocorticoid receptor antagonist is effective at treating psychosis caused by side effects of a medication. Furthermore, although Schatzberg et al. do not teach using the glucocorticoid receptor antagonist concomitantly with the interferon- α and ribavirin, it would have been obvious to one of ordinary skill in the art because it provides the patient protection against developing psychosis throughout the IFN- α treatment. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed August 22, 2008 have been fully considered but they are not persuasive.

Applicant argues that neither Schatzberg nor Ademmer suggest that IFN- α has any effect on glucocorticoid signaling or regulation and therefore one of ordinary skill in the art would not expect that a glucocorticoid receptor antagonist (GRA) would successfully treat the particular psychoses related to IFN- α treatment.

This argument is not persuasive. Schatzberg et al. teach that the pathophysiology of psychosis is related to neurochemical (glucocorticoid regulatory) problems and that inhibiting the binding of cortisol to its receptor (by administration of a GRA) can be used to treat psychosis (see column 1 lines 43-49 and column 2 lines 9-20). Schatzberg et al. also teach that psychosis not only refers to a psychiatric symptom or condition, but also a symptom associated with the side effects of a medication (see column 6 lines 26-35). Thus, it is established that psychosis is associated with glucocorticoid dysfunction and that treating psychosis (and symptoms) as a result of side effects of a medication (e.g. IFN- α), with a GRA is a known concept in the art. Furthermore, Ademmer teaches psychosis symptoms in patients undergoing IFN- α treatment. Therefore, it would have been obvious to try to treat the symptoms of psychosis associated with IFN- α treatment with a GRA.

Applicant has not provided any evidence to support that the symptoms of psychosis associated with IFN-α treatment would be different from the psychosis (and

symptoms) taught in the prior art and Attorney's arguments cannot take place of evidence (see MPEP 716.01(c)).

Applicant provided a 1.132 declaration that discloses that mifepristone is effective in treating patients suffering from psychotic major depression but has no clinical benefits for psychotic patients suffering from schizoaffective disease.

However, this is not persuasive. Applicant has not provided evidence that distinguishes that psychosis associated with IFN-α therapy is different from the psychosis taught in the prior art. Applicant provided evidence of what is already known and taught in the prior art reference Schatzberg et al. (see 103 rejections above). And that is that schizophrenia and manic states are not intended to be treated by a GRA (see Schatzberg et al., column 1 lines 29-32 and 57-61, column 6 lines 67, and column 77 lines 1-11).

Next, Applicant argues that Ademmer does not disclose that psychotic symptoms are included in the psychiatric symptoms (i.e. depression, suicide ideation) experienced by IFN- α patients.

It should be noted that Applicant does not define what "symptoms of psychosis" Applicant intends in claim 1. Thus, the phrase "symptoms of psychosis" is broadly construed and is encompassed by psychiatric symptoms, as taught in Ademmer, especially in absence of evidence to the contrary.

It is noted that the features upon which applicant relies (i.e. link between IFN- α and glucocorticoid regulation,) are not recited in the rejected claim(s). However, it is well known in the art that IFN- α therapy causes an increase in serum cortisol levels (as evidenced by Shimizu et al, Increase in serum interleukin-6, plasma ACTH and cortisol levels after systemic interferon-α administration, Endocrine Journal, 42(4):551-6, 1995, abstract). Thus, one of ordinary skill in the art would recognize that IFN- α does play a role in glucocorticoid regulation, further establishing motivation for the use of a GRA, since an increase in cortisol levels are known to cause psychosis or symptoms of psychosis as suggested by Schatzberg et al.

Therefore, Applicants arguments of non-obviousness are not persuasive and the rejection is maintained.

6. Claims 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schatzberg et al. (US 6,150, 349) in view of Ademmer et al. (Suicidal Ideation with IFN-α and Ribavirin in a Patient with Hepatitis C, *Psychosomatics* 42:4, 365-367, 2001) further in view of Dieterich (Treatment of Hepatitis C and Anemia in Human Immunodeficiency Virus-Infected Patients, The Journal of Infectious Diseases, 185(Suppl 2):S128-37, 2002)

Applicant claims a method of ameliorating the symptoms of psychosis associated with interferon-α therapy in a patient comprising administering to the patient having received interferon-α therapy and suffering from psychosis associated with the

interferon- α therapy, an amount of a glucocorticoid receptor antagonist effective to ameliorate the symptoms of psychosis in the patient, with the proviso that the patient is not otherwise in need of treatment with a glucocorticoid receptor antagonist.

Determination of the scope and content of the prior art

(MPEP 2141.01)

The disclosure of Schatzberg et al. is set forth above. Specifically, Schatzberg et al. teach a method of ameliorating psychosis to patient in need thereof comprising administering an effective amount of a glucocorticoid receptor antagonist.

The disclosure of Ademmer et al. is set forth above. Specifically Ademmer et al. teach the state of the art treatment for hepatitis C virus (HCV) is the combination therapy with interferon alpha (IFN- α) and ribavirin. And that one of the most serious side effects of the IFN- α treatment is the development of psychiatric symptoms, particularly depression and suicide ideation.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Schatzberg et al. and Ademmer do not teach ameliorating the symptoms of psychosis associated with a patient having received interferon- α therapy and is suffering from leukemia, HIV, Human T-Cell Lymphotropic virus or cancer or has a history of substance abuse. This deficiency is cured by the teachings of Dieterich.

Dieterich teaches that co-infection of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) is common, especially among intravenous drug abusers (see the entire article, especially the second paragraph under the introduction). Patients receiving IFN- α and ribavirin therapy can experience side effects such as influenza-like syndrome and other side effects that persist or increase with continued treatment such as neuropsychiatric effects including depression, anxiety, personality change etc (see the entire article, especially page S134, the third paragraph in the first column and the second and third paragraph in the second column).

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to ameliorate the symptoms of psychosis associated with a patient having received interferon- α therapy and is suffering HIV and has a history of substance abuse comprising administering a glucocorticoid receptor antagonist.

One of ordinary skill in the art would have been motivated to do this because Dieterich suggest that it is common for a patient to be co-infected with HCV and HIV, especially among intravenous drug users. It is also known that co-infected patients treated with interferon- α and ribavirin can develop neuropsychiatric effects such as

depression. Thus, it would have been obvious to one of ordinary skill in the art to treat a co-infected patient who has a history of substance abuse receiving IFN- α treatment with a glucocorticoid receptor antagonist because are they are still prone to developing side caused by side effects of the medication (i.e. IFN- α treatment). Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed August 22, 2008 have been fully considered but they are not persuasive.

Applicant argues that Schatzberg, Ademmer and Dietrich fail to link IFN- α to glucocorticoid regulation. Applicant further argues that the neurophyschiatric symptoms taught in Dietrich are broad and would not be automatically inclusive of psychotic symptoms.

These arguments are not convincing. First, it is noted that the features upon which applicant relies (i.e. link between IFN- α and glucocorticoid regulation,) are not recited in the rejected claim(s). However, it is well known in the art that IFN- α therapy causes an increase in serum cortisol levels (as evidenced by Shimizu et al, Increase in serum interleukin-6, plasma ACTH and cortisol levels after systemic interferon-α administration, Endocrine Journal, 42(4):551-6, 1995, abstract). Thus, one of ordinary skill in the art would recognize that IFN- α does play a role in glucocorticoid regulation,

further establishing motivation for the use of a GRA, since an increase in cortisol levels are known to cause psychosis or symptoms of psychosis as suggested by Schatzberg et al.

Furthermore, Applicant does not define what "symptoms of psychosis" Applicant intends in claim 1. Thus, the phrase "symptoms of psychosis" is broadly construed and is encompassed by neuropsychiatric symptoms, as taught in Dietrich, especially in absence of evidence to the contrary.

Therefore, Applicants arguments of non-obviousness are not persuasive and the rejection is maintained.

Conclusion

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kristie L. Brooks whose telephone number is (571) 272-9072. The examiner can normally be reached on M-F 8:30am-6:00pm Est..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KB

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616